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(54) Enteric microcapsules and process for the preparation thereof.

(57) Novel enteric microcapsules containing an active compound as a core material, the coating walls of which consist essentially of ethylcellulose and an enteric polymer material, and optionally a water-swellable polymer material being incorporated into the core material, and a process for the preparation thereof. The microcapsules can easily release the active compound in intestinal tract while protecting the core material sufficiently in stomach.

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ENTERIC MICROCAPSULES AND PROCESS FOR THE PREPARATION THEREOF

The present invention relates to novel enteric microcapsules and a process for the preparation thereof, more particularly, to enteric microcapsules containing an active compound as a core material, the coating walls of which consist essentially of ethylcellulose and an enteric polymer material, and a process for the preparation thereof.

It is known to control the release of a core material in microcapsules by thickening the coating walls of microcapsules or by forming compact coating walls and thereby decreasing the permeability thereof (cf. Tamotsu Kondo and Masumi Koishi; "Microcapsules, Process for the Preparation thereof, Their Properties and Applications", issued by Sankyo Shuppan, 1977). According to these known methods, however, while the release of core material is well controlled, the release of core material is also inhibited even when the core material should be released and hence the desired activities of the main active compounds are occasionally not obtained. Particularly, in case of pharmaceutical compounds, they are usually microencapsulated with ethylcellulose in order to mask unpleasant odor or taste thereof, but in most cases, such microcapsules show

retarded release of the active ingredient in intestinal tract.

From this viewpoint, the present inventors have extensively studied on improvement of microcapsules, and as a result, it has been found that the desired enteric microcapsules having excellent effect of protecting the core material and being capable of releasing easily the core material in intestinal tract can be obtained by incorporating an enteric polymer material into the ethylcellulose coating walls of microcapsules containing core material, or incorporating a water-swellable polymer material into the core material contained in the microcapsules and further incorporating an enteric polymer material into the ethylcellulose coating walls.

An object of the present invention is to provide enteric microcapsules being capable of releasing easily the active component (core material) in intestinal tract while protecting the core material effectively in stomach. Another object of the invention is to provide a process for the preparation of the enteric microcapsules. These and other objects and advantages of the present invention will be apparent to persons skilled in the art from the following description.

The novel enteric microcapsules of the present invention (i.e., enteric microcapsules containing an active compound as a core material, the coating walls of which

consists essentially of ethylcellulose and an enteric polymer material) can be prepared by the steps of:

(a) dissolving ethylcellulose in a solvent,

(b) dispersing particles of a core material in the solution thus obtained,

(c) cooling the dispersion until coating walls having a viscosity of 0.1 to 50 P are formed on and around the particles of the core material,

(d) adding an enteric polymer material to the dispersion,

(e) further cooling the dispersion containing the enteric polymer material until the resultant embryonic microcapsules shrink and become solid by solvent loss from the coating walls, and then

(f) recovering the thus-formed microcapsules therefrom.

The core material used in the present invention includes pharmaceutical compounds and foodstuffs which may be in the form of a solid, gel or semi-solid. The particle size of the core material is not critical but is usually in the range of about 30 to 1,000 μ, preferably about 50 to 500 μ.

Ethylcellulose used for forming microcapsule coating walls on and around the particles of the core material has preferably an ethoxy content of about 46.5 to 55 W/W % and a viscosity of about 3 to 500 cP (the viscosity of ethylcellulose is measured in a 5 W/W %

solution in toluene-ethanol (4 : 1) at 25°C). The ethylcellulose is usually used in an amount of about 0.01 to 10 grams per gram of the core material.

The enteric polymer material to be incorporated into the ethylcellulose coating walls includes (i) an organic dicarboxylic acid ester of a hydroxyalkyl alkylcellulose or cellulose acetate; (ii) a carboxyalkyl alkylcellulose; (iii) a copolymer of an alkenylcarboxylic acid and an alkyl ester of an alkenylcarboxylic acid; (iv) a copolymer of an alkenylcarboxylic acid and two alkyl esters of an alkenylcarboxylic acid, (v) zein and (vi) shellac. Suitable examples of the organic dicarboxylic acid esters of a hydroxyalkyl alkylcellulose or cellulose acetate (i) are phthalic acid esters of a hydroxyalkyl alkylcellulose or cellulose acetate, such as hydroxyethyl ethylcellulose phthalate, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, and other organic dicarboxylic esters such as cellulose acetate succinate, cellulose acetate maleate, or the like. Suitable examples of the carboxyalkyl alkylcellulose (ii) are carboxymethyl methylcellulose and carboxymethyl ethylcellulose. Suitable examples of the copolymer of an alkenylcarboxylic acid and an alkyl ester of an alkenylcarboxylic acid (iii) are copolymers of methacrylic acid and an alkyl acrylate or methacrylate, such as a copolymer of methacrylic acid and methyl acrylate, a copolymer of methacrylic acid and ethyl

acrylate, copolymer of methacrylic acid and methyl methacrylate. Suitable examples of the copolymer of an alkenylcarboxylic acid and two alkyl esters of an alkenylcarboxylic acid (iv) are copolymers of methacrylic acid, an alkyl acrylate and an alkyl methacrylate, such as a copolymer of methacrylic acid, methyl acrylate and methyl methacrylate, a copolymer of methacrylic acid, methyl acrylate and octyl acrylate.

These enteric polymer materials are preferably in the form of a finely-divided particle, particularly having a particle size of about 300 μ or less, more particularly a particle size of 0.1 to 300 μ. The enteric polymer materials are preferably used in an amount of at least about 0.01 gram, more preferably about 0.05 to 20 grams per gram of the coating wall-forming material (ethylcellulose).

When a water-swellable polymer material is incorporated into the core material in microcapsules wherein an enteric polymer material is incroporated in the coating walls, the release of the active compound is more promoted.

Such a water-swellable polymer material is a material which shows at least 1.2 times increase in weight by immersing it in water at 37°C. The water-swellable polymer material includes agar-agar, pectinic acid, alginic acid, cellulose, starch, a carboxyalkyl cellulose (e.g. carboxymethyl cellulose) or its calcium

salt, copolymers of divinylbenzene and an alkenylcarboxylic acid (e.g. a copolymer of divinylbenzene and acrylic acid, a copolymer of divinylbenzene and methacrylic acid), a cross-linked gum arabic (e.g. gum arabic cross-linked with epichlorohydrin), a cross-linked dextran (e.g. dextran cross-linked with epichlorohydrin), and a cross-linked polyalkenylcarboxylic acid (e.g. self-crosslinked polyacrylic acid, self-cross-linked methacrylic acid).

These water-swellable polymer materials are preferably in the form of a finely-divided particle, particularly having a particle size of about 300 μ or less, more particularly a particle size of 0.1 to 300 μ. Suitable amount of the water-swellable polymer material to be incorporated into the core material is about 1 to 99 w/w %, especially about 5 to 90 w/w %.

In the preparation of the microcapsules of the present invention, an ethylcellulose dispersion containing a core material is firstly prepared by dispersing a core material into a solution containing ethylcellulose as the wall-forming material. In case of ethylcellulose microcapsules containing a water-swellable polymer material in the core material, it is preferable to previously prepare a granule of a mixture of a core material and a water-swellable polymer material, and the core material containing a water-swellable polymer material is dispersed into

Example 2

(1) To a mixture of trimethoquinol hydrochloride (chemical name: ℓ-1-(3,4,5-trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride) (25 parts), lactose (45 parts), white dextrin (10 parts) and a water-swellable polymer material as shown in Table 4 (20 parts) was added a 40 % aqueous ethanol (10 parts), and the mixture was kneaded in a usual manner to give granules. The granules were dried and regulated to a particle size of 105 to 210 μ.

(2) To cyclohexane (600 ml) were added a mixture of two polyisobutylenes (molecular weight: 50,000 and 1,200,000, respectively, 1 : 1 by weight) (18 g) and the same ethylcellulose as used in Experiment I (12 g), and the mixture was dissolved by heating at 80°C. After dispersing the core material as obtained in the above (1) (48 g) to the solution, the dispersion was cooled with stirring at 400 r.p.m. When the temperature became to about 65°C, cellulose acetate phthalate (acetyl content: 20.8 %, carboxybenzoyl content: 34.5 %) (60 g) was added in order to incorporate it into the coating walls and then the mixture was cooled to room temperature. The microcapsules thus formed were separated washed with n-hexane and dried. Said microcapsules were treated in the same manner as described in Example 1 to give trimethoquinol hydrochloride-containing microcapsules.

wherein particles of the core material contain a water-swellable polymer material which shows at least 1.5 times increase in weight by immersing it in water at 37°C.

10. The microcapsules according to claim 9, wherein the water-swellable polymer is a member selected from the group consisting of agar-agar, pectinic acid, alginic acid, cellulose, starch, a carboxyalkyl cellulose, a carboxyalkyl cellulose calcium, a copolymer of divinylbenzene and an alkenylcarboxylic acid, a cross-linked gum arabic, a cross-linked dextran, and a cross-linked polyalkenylcarboxylic acid.

11. The microcapsules according to claim 9, wherein the water-swellable polymer is a member selected from the group consisting of agar-agar, pectinic acid, alginic acid, cellulose, starch, carboxymethyl cellulose, carboxymethyl cellulose calcium, copolymer of divinylbenzene and acrylic acid, gum arabic cross-linked with epichlorohydrin, dextran cross-linked with epichlorohydrin, and self-crosslinked polyacrylic acid.

12. A method of preparing ethylcellulose microcapsules which comprises the steps of:

(a) dissolving ethylcellulose in a solvent,

(b) dispersing particles of a core material in the solution thus obtained,

(c) cooling the dispersion until coating walls having a viscosity of 0.1 to 50 P are formed on and